I. Double Patenting

Claim 1 has been rejected under the judicially created doctrine of obviousness-typ double patenting as being unpatentable over claim 13 of U.S. Patent 6,228,642. The Examiner suggests that although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are drawn to a method of antisense-mediated inhibition of TNF-α *in vivo*. Applicants are filing herewith a terminal disclaimer as required under 37 CFR 1.130(b). Accordingly, withdrawal of this rejection is respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 1 and 3-11 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is enabling for treatment of colitis and rheumatoid arthritis using antisense compound ISIS 25302. However, the Examiner suggests that the specification provides no other examples

of antisense activity as claimed other than with ISIS 25302. The Examiner cites several articles to support the view that application of antisense *in vivo* is unpredictable. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed *in vivo* with one antisense compound of the instant invention would not also occur with other antisense compounds of the instant invention.

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. However, the statements pointed to by the Examiner concerning the unpredictability of antisense in terms of extrapolating from data in cells to data *in vivo* do not apply here since the data for at least one of the compounds of the

instant invention have been shown to support such an extrapolation for other related compounds. It is a fundamental principle of drug development that data from cell studies, such as are provided in Example 15 of the instant specification, are directly applicable to predicting *in vivo* activity. More importantly, when one compound of a class of compounds has been shown to be active *in vivo*, it is a general principle of pharmacology that other compounds with similar *in vitro* activity will also be active *in vivo*. The specification as filed provides data showing *in vitro* activity of many compounds and how *in vitro* activity correlates with *in vivo* activity. The teachings of the paper by Crooke provide no reason to doubt that these fundamental principles are applicable to antisense agents of the instant invention.

In fact, statements in the paper by Crooke support the fact that development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [in vitro]." The key according to Crooke is the careful design of

the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the reference does the author state or suggest that results of well-designed pharmacological studies for a particular compound of a class would not be predictive of activity *in vivo* for other compounds of that same class.

Moreover, the paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable, nor that data in vivo for one compound is not predictive of activity of similar compounds in the class.

The paper by Agrawal et al. is a review paper from 1996 on the technology of antisense. Like the papers discussed above, nowhere does this paper state that extrapolation from *in vitro* data

to *in vivo* effects is unpredictable, nor that data in vivo for one compound is not predictive of activity of similar compounds in the class.

The paper by Gewirtz et al. (1996) is another older paper on antisense technology that is not relevant to the state of the art of antisense in 2000, the filing of the instant application. Like the other papers cited by the Examiner, this paper only reviews issues that have arisen during development of the technology. Nowhere does this paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable, nor that data in vivo for one compound is not predictive of activity of similar compounds in the class.

In an earnest effort to advance the prosecution of this case, Applicants have amended claim 1 to recite that the compounds are for treatment of colitis or rheumatoid arthritis, the two inflammatory conditions where a compound directed to inhibition of TNF-α was shown to be effective *in vivo*. Withdrawal of the rejection is requested in light of this amendment to the claims.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **September 9, 2002**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 4 has been canceled.

The claims have been amended as follows:

1. (amended) A method of treating ~~an inflammatory disorder~~ colitis or rheumatoid arthritis in an individual comprising administering to ~~said~~ an individual an effective amount of an oligonucleotide up to 30 nucleotides in length complementary to a nucleic acid molecule encoding human tumor necrosis factor-α (SEQ ID NO: 1).

6. (amended) The method of claim ~~4~~ 5, wherein said intersugar linkage is a phosphorothioate linkage.